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NEPHROLOGY FORUM

Lipids and the kidney

Principal discussant: WILLIAM F. KEANE

Hennepin County Medical Center and University of Minnesota, Minneapolis, Minnesota

Case presentation

A 28-year-old white man was evaluated for progressive deterioration of renal function. At age 17, he presented with symptoms of the nephrotic syndrome. Evaluation at that time included a blood pressure of 135/90 mm Hg; serum creatinine, 1.5 mg/dl; creatinine clearance, 81 ml/min; urine protein, 6.3 g/24 hr; serum albumin, 3.1 g/dl; serum cholesterol, 325 mg/dl; triglycerides, 220 mg/dl; low-density lipoprotein (LDL) cholesterol, 240 mg/dl; and a high-density lipoprotein (HDL) of 32 mg/dl. A renal biopsy demonstrated histopathologic changes consistent with focal and segmental glomerulosclerosis. The patient was treated briefly with a course of prednisone without clinical benefit. His blood pressure was effectively treated with various antihypertensive agents and was usually recorded as < 160/90 mm Hg during followup visits. Modest dietary protein restriction was also prescribed, although his adherence was questionable. Despite these efforts, his renal function progressively deteriorated over the ensuing 11 years, proteinuria ranged from 3 to 6 g/24 hr, and marked hyperlipidemia persisted. During the past 6 months, he has noted left-sided chest pain, particularly when he was physically active.

Physical examination revealed a chronically ill man who appeared older than his stated age. His supine blood pressure was 165/95 mm Hg, and his pulse was 88 beats/min and regular. Funduscopic examination revealed increased light reflex and modest arteriovenous nicking but no hemorrhages or exudates. Chest examination was unremarkable and the cardiac examination revealed only an S4 gallop. There was no jugular venous distention. Abdominal examination was unremarkable and ascites was not present. Extremities revealed only trace edema, and the rest of the neurologic examination was unremarkable.

Fasting laboratory studies revealed a creatinine clearance of 15 ml/min with a serum creatinine of 6.3 mg/dl. Urinary protein was 4.7 g/24 hr. Total cholesterol was 315 mg/dl; LDL cholesterol, 248 mg/dl; HDL cholesterol, 25 mg/dl; triglycerides, 455 mg/dl; and lipoprotein (a) [Lp(a)], 120 mg/dl. Serum albumin was 3.0 g/dl. An electrocardiogram showed nonspecific ST-segment and T-wave abnormalities. An exercise tolerance test revealed significant ST-segment depression in the inferior leads. Coronary angiography demonstrated an isolated lesion of the circumflex vessel estimated to represent an 85% stenosis.

A diagnosis of chronic renal failure secondary to focal glomerulosclerosis with persistent nephrotic-range proteinuria and marked dyslipidemia was confirmed. In addition, significant coronary artery disease was diagnosed. Blood pressure was returned to normal with the addition of an angiotensin-converting-enzyme inhibitor. On this regimen, his proteinuria decreased to 2.2 g/24 hr over the next 3 months. The LDL cholesterol also decreased to 218 mg/dl. Because of the persistent hyperlipidemia and evidence of atherosclerosis, lovastatin (10 mg at bedtime) was initiated.

Discussion

DR. WILLIAM F. KEANE (*Professor and Chairman, Department of Medicine, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, Minnesota*): The case before us today raises a number of important clinical issues regarding the role of secondary hyperlipidemia in vascular injury in humans. Although we lack a clear-cut scientific understanding of its role clinically, considerable experimental evidence implicates hyperlipidemia as a factor in the progressive nature of proteinuric renal disease [1, 2]. We must address several clinically important questions. Are patients with proteinuric renal diseases and secondary hyperlipidemia at greater risk for the early development of coronary artery disease? If so, can aggressive therapeutic intervention reduce this risk? Does hyperlipidemia contribute to the progression of renal disease in humans and, if so, how? Does lipid-lowering therapy retard the progression of human renal disease? If so, by what mechanism(s)?

Cardiovascular implications of dyslipidemia associated with proteinuria

Patients with diabetes or essential hypertension who have even small increases in urinary albumin concentration (microalbuminuria) are at significantly greater risk for increased cardiovascular morbidity and mortality [3, 4]. It is not known whether microalbuminuria causes metabolic derangements that, in turn, are responsible for the patient's greater propensity to develop cardiovascular disease, or whether microalbuminuria is simply the expression of more generalized cardiovascular disease that involves the kidneys as well. Recent epidemiologic studies have, however, found atherogenic abnormalities in the lipid profiles of type-I and type-II diabetic patients as well as patients with essential hypertension and microalbuminuria [5–7]. Increased LDL cholesterol and increased Lp(a) have been reported in a number of studies [8,

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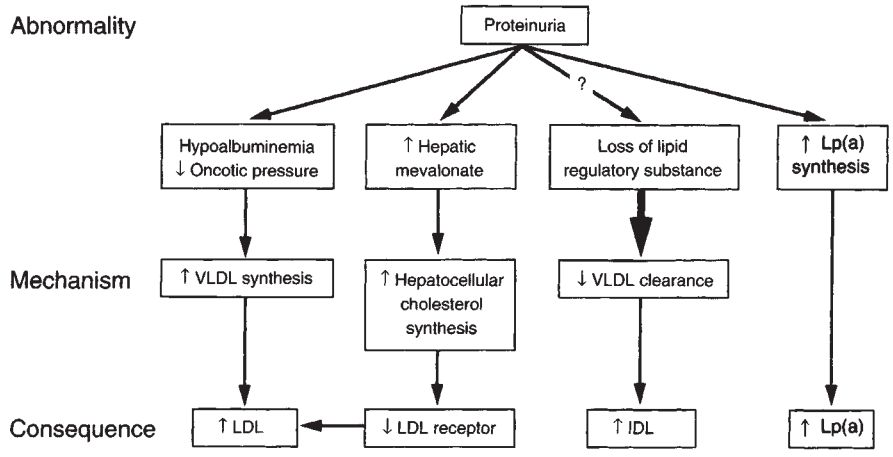

Fig. 1. *Potential effects of proteinuria on dyslipidemia in the nephrotic syndrome.* Abbreviations are: VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; Lp(a), lipoprotein a: ↑, increase; ↓, decrease; ?, questionable. (From Ref. 11.)

9]. In addition, type-I and type-II diabetic patients with microalbuminuria frequently have reduced levels of HDL cholesterol [8–10]. These abnormalities in lipid profiles occur early in the clinical course of patients with diabetes or essential hypertension, usually long before clinical evidence of cardiovascular disease exists; these lipid abnormalities thus might have pathogenetic implications. The mechanism(s) whereby subtle changes in the permselective nature of the filtration barrier contribute to the lipid changes is unknown. It is possible, however, that genetic factors link these two abnormalities [5]. Alternatively, the kidneys themselves might play an important regulatory role in lipid metabolism, which is disturbed with the onset of proteinuria.

As in the case today, nondiabetic patients with overt proteinuria nearly always have marked abnormalities in their lipid profiles [11] (Fig. 1); increased LDL cholesterol is the main lipid defect seen in patients with nephrotic-range proteinuria [11]. Alterations in LDL composition, including phospholipids and cholesterol esters as well as increased apolipoprotein (apo) B, have been described. The level of HDL in nephrotics has been reported as high, normal, or low. In patients with elevated triglycerides, as in the patient today, HDL levels usually are reduced [11]. Even when the levels of HDL are normal, the HDL subtypes are abnormally distributed; specifically, the level of HDL-2 usually is reduced, whereas HDL-3 is elevated. Elevated triglyceride levels are frequently seen, especially in patients with severe proteinuria or reduced renal function. Patients with overt proteinuria also have elevated Lp(a) levels [12].

The mechanisms of these lipid abnormalities in proteinuric patients are incompletely understood, but increased synthesis and altered receptor-dependent and receptor-independent catabolism have been demonstrated [13, 14] (Fig. 1). Moreover, recent experimental studies have suggested a direct link between lipid abnormalities and proteinuria [15]. In these studies, expression of hypercholesterolemia corresponded to the onset of proteinuria and usually occurred prior to the onset of reduced serum albumin levels [15]. Further support for a relationship between proteinuria and dyslipidemia has been provided by studies in which pharmacologic reduction in proteinuria was accompanied by a reduction in LDL cholesterol and Lp(a) [16]. Indeed, in today's patient, cholesterol decreased in association with a decline in proteinuria.

Whether nondiabetic patients with persistent proteinuria have an increased risk for atherosclerosis has been debated for decades [11]. During the past few years, renewed interest has emerged regarding the importance of cardiovascular disease in patients with proteinuria. In a preliminary report of nondiabetic adults with proteinuria, the relative risk for acute myocardial infarction and death due to coronary artery disease was more than fivefold greater than in age- and gender-matched, nondiabetic control patients [17]. Moreover, in children and young adults with proteinuric renal disease who died at a mean age of 14.9 ± 7.7 years, more than 75% had evidence of atherosclerosis at autopsy, and 13% had greater than 50% coronary artery occlusions [18]. Unfortunately, lipid analyses were not routinely performed in these patients. These findings are reminiscent of earlier sporadic case reports in children with the nephrotic syndrome and atherosclerosis [19]. The paucity of prospective epidemiologic data, and the glaring absence of dietary or pharmacologic studies designed to reduce circulating lipids and assess cardiovascular end points, make specific therapeutic recommendations difficult. Nonetheless, if clinical experience in one area can be transferred to other areas, it seems prudent that efforts be directed toward the reduction of atherogenic lipids in patients with persistent proteinuria. The available experiences with the various lipid-lowering agents have been reviewed recently [11, 20].

Do lipids contribute to progressive renal injury?

The relationship between lipid abnormalities and renal disease has not been studied rigorously. We do have some preliminary data, however. The incidence of renal disease in patients with the most common forms of primary hyperlipidemia, although unknown, is low. One recent report suggested that the prevalence of microalbuminuria in patients with primary lipid disorders is not increased [21]. On the other hand, autopsy studies have noted a significant relationship between global glomerulosclerosis and atherosclerosis and have suggested a relationship between factors that contribute to atherosclerosis and those leading to glomerulosclerosis [22]. These clinical observations are consistent with experimental studies in which lipid abnormalities are predominantly seen as modulators of progressive renal disease rather than as primary initiators of renal disease. We should remember, however, that a number of unique abnormalities of lipid metabolism, such as those in patients with lecithin-cholesterol acyltransferase deficiency, are associated with the development of renal disease. A few case reports have detailed a unique form of

nephrotic syndrome associated with aneurysmal dilation of glomerular capillaries, lipoprotein-containing thrombi in glomerular capillaries, mesangial expansion, mesangial proliferation, and glomerulosclerosis associated with increased circulating levels of apo E [23, 24]. This form of renal disease, termed lipoprotein glomerulopathy, has been observed in patients without elevated serum cholesterol levels but in whom apo E levels are increased [25]. Deposits of apo B and apo E also have been seen by immunohistochemical techniques in other forms of proteinuric renal diseases, such as IgA nephropathy [26, 27]. In addition, foam cells frequently are found in segments of glomeruli undergoing sclerosis in patients with focal glomerulosclerosis [1]. Foam cells are believed to result from non-receptor-mediated uptake of modified lipoproteins by macrophages. The finding of lipoproteins and foam cells in glomeruli of patients with proteinuria suggests that lipoproteins might be oxidatively modified, an alteration that could enhance binding to matrix proteins and result in local glomerular mesangial deposits [28]. Additional studies will be needed to support this hypothesis.

Preliminary reports have suggested a relationship between lipids and the rate of progression of renal disease. In nondiabetic patients with proteinuria, hypercholesterolemia, and hypertriglyceridemia, the rate of loss of renal function was nearly twofold greater than in patients without marked hyperlipidemia [29]. This effect was independent of blood pressure control. In addition, in black and Hispanic children with the nephrotic syndrome secondary to focal glomerulosclerosis, the level of cholesterol at presentation predicted the time to renal failure [30]. Similarly, in a group of nondiabetic, proteinuric patients with progressive renal insufficiency, the rate of loss of renal function was twice as great in patients with elevated lipid levels as in those with normal lipid levels [31]. The most dramatic association seen was between elevated apo B levels and a monthly decline in glomerular filtration rate [31]. In addition, these investigators demonstrated a positive correlation between hypertension and hyperlipidemia.

In type-I diabetic patients with nephropathy, total and LDL cholesterol levels were independent risk factors for the progression of renal disease [32]. As in patients with nondiabetic disease, a correlation also existed between hypertension and hyperlipidemia, and both together influenced the progression of renal disease [32].

A recent retrospective analysis of type-I diabetic patients enrolled in the Diabetic Retinopathy Study also discerned a relationship between loss of renal function and hypercholesterolemia [33]. Recently, Walker reported an association between cholesterol and angiotensin II levels in 131 diabetic subjects followed for as long as 8 years [34]. Although no clear-cut relationship could be established between the rate of loss of renal function and hyperlipidemia in this study, the strong interaction with angiotensin II and blood pressure (the latter being the principal determinant of progression) likely suggests an important secondary role of cholesterol [34]. To date, no prospective study has been performed that demonstrates the relationship between the progression of renal disease and the degree of hyperlipidemia in either diabetic or nondiabetic patients.

Therapeutic trials aimed at reducing circulating lipids have, in large part, been short-term studies designed more to evaluate safety and efficacy of a diet or a specific antilipemic agent [11]. In diabetic and nondiabetic patients, antilipemic agents have been effective in reducing cholesterol; specific recommendations for a given class of agents are best determined by the type of abnormality in the lipid profile of the patient. In the patient discussed today, a low dose of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor was selected. Data from clinical trials would lead one to expect a significant reduction in LDL cholesterol, probably a smaller decrease in triglycerides, and a modest increase in HDL cholesterol [11]. Whether this class of antilipemic agent will influence the rate of loss of renal function remains to be determined. Justification for this approach can be gathered from a number of uncontrolled preliminary reports in diabetic and nondiabetic proteinuric patients with progressive renal disease [35–38]. These studies generally have used HMG-CoA reductase inhibitors and have demonstrated a reduction in circulating cholesterol levels and stabilization or improvement of renal function [35–38]. As I mentioned earlier, the impact of these agents on cardiovascular disease is unknown.

Table 1. Animal models of lipid-induced renal injury

Models	Renal damage
Dietary-induced hyperlipidemia	+[a]
Rat	+
Guinea pig	+
Rabbit	+
Diet-induced hyperlipidemia and another underlying disorder	
Rat, unilateral nephrectomy	++
Rat, clip hypertension	
Clipped kidney	+
Unclipped kidney	+++
Genetic hyperlipidemia	
Obese Zucker rat	++
Spontaneous hypertensive obese rat	+++
Secondary hyperlipidemia	
Dahl salt-sensitive rat	++
Rat, remnant kidney model	++
Rat, chronic nephrosis	++

[a] Abbreviations: +, moderate; ++, intermediate; +++, severe.

Modulation of glomerular injury by lipids: Experimental insights

As I stated at the outset, experimental investigations have suggested that lipids are involved in renal injury (Table 1). First, studies in several animal models of renal disease have demonstrated an association between circulating cholesterol levels and indices of glomerular injury, including the degree of glomerulosclerosis, mesangial expansion, and hyalinosis [39]. These studies also demonstrated a highly significant relationship between cholesterol and glomerular deposits of lipids [39]. Indeed, failure to detect glomerular lipid deposits was associated with minimal glomerulosclerosis despite hypercholesterolemia [40]. These studies provide only a useful framework for conceptualizing the pathogenetic events that might have contributed to glomerulosclerosis and do not indicate causality.

More direct evidence that hyperlipidemia can contribute to glomerular injury has come from studies of diet-induced hypercholesterolemia in a variety of normal animals. In our studies, feeding rats a 4% cholesterol-supplemented diet for 3 months resulted in glomerular enlargement, mesangial expansion and hypercellularity, albuminuria, and a modest degree of focal glomerulosclerosis [41]. The expanded mesangial matrix was constituted primarily by type-IV collagen, fibronectin, and laminin [42]. The increased mesangial cellularity was in part a result of an

Table 2. Lipid-lowering agents that have reduced renal injury in different animal models

Drug	Animal model
Cholestyramine	Chronic puromycin nephrosis
Clofibrate	Remnant kidney model
	Obese Zucker rat
Lovastatin	Chronic puromycin nephrosis
	Remnant kidney model
	Obese Zucker rat
	Dahl salt-sensitive rat
Probucol	Chronic puromycin nephrosis
	Remnant kidney model

increased influx of macrophages, which preceded mesangial expansion and albuminuria [42]. Foam cells also were evident, as was an increased glomerular deposition of lipids. Biochemical analysis of glomerular lipids demonstrated an increased concentration of cholesterol esters and a reduced concentration of polyunsaturated fatty acids; these findings suggested the presence of oxidatively modified lipids [41]. Although the degree of renal injury seen in these studies was modest, it indicated a potentially important relationship between lipids and the glomerular recruitment of macrophages as well as glomerular mesangial cell proliferation. In addition, these studies suggested a relationship between hypercholesterolemia and accumulation of glomerular matrix proteins, as well as a potential role for oxidatively modified lipids in progressive glomerular injury. When diet-induced hypercholesterolemia was combined with hypertension in rats with Goldblatt hypertension or in hypertensive Dahl salt-sensitive rats, glomerular injury markedly increased [43, 44]. Similarly, reduction in nephron number [41] or induction of the nephrotic syndrome by puromycin aminonucleoside [45] was associated with exacerbation of glomerular injury in cholesterol-fed rats.

A third series of experiments that has supported a role for hyperlipidemia in progressive renal injury involves investigations in which lipid-lowering agents were used (Table 2). In the remnant kidney model of progressive renal failure, induced by surgical removal of 80% to 90% of renal mass, hypertension, proteinuria, mesangial expansion, and increased mesangial cellularity all occurred prior to the development of glomerulosclerosis. Treatment with either an HMG-CoA reductase inhibitor or clofibric acid reduced serum lipids, diminished albuminuria, decreased mesangial cellularity and matrix expansion, and significantly reduced the incidence of glomerulosclerosis [46–49]. The effects of these agents occurred independently of any influence on systemic or glomerular hypertension, thus suggesting a mechanism of action independent of lowering of blood pressure. Probucol, a cholesterol-lowering drug with antioxidant properties, also ameliorated renal injury in this experimental model, and thus raised a potentially important pathogenetic role for oxidant injury [50].

In the obese Zucker rat, a model of endogenous hyperlipidemia with features similar to non-insulin-dependent diabetes mellitus, mesangial expansion, increased mesangial cellularity, increased glomerular macrophages, glomerular lipid deposits, and albuminuria also precede the development of glomerulosclerosis [51]. In this model, anti-lipemic therapy also reduced lipids, mesangial expansion and cellularity, and the incidence of glomerulosclerosis [47]. Again, these actions of anti-lipemic drugs occurred independently of systemic or glomerular hemodynamic effects, thus suggesting a nonhemodynamic role for lipids in the development of glomerular injury in this model [47, 52]. To better assess the potential interactions between the glomerulus and cholesterol, investigators recently have directed their attention to evaluating the interactions between mesangial cells and lipids. Wide-ranging in-vitro studies have shed light on the interactions between mesangial cells and lipids. Many of these interactions are summarized in Figure 2.

Influence of lipids on mesangial cell proliferation. Glomerular mesangial and epithelial cells possess receptors for LDL [53–57]. The binding of LDL to these cells, saturable at 4°C, is inhibitable by heparin and excess LDL; the process is similar to the LDL receptor binding observed in other cells [53, 56]. In addition, LDL binds to many discrete membrane sites that aggregate and are internalized [53]. These observations are consistent with the process of receptor-mediated endocytosis of receptor-bound LDL and intracellular endosomal and lysosomal processing as described for LDL receptors in other cells [53]. Regulation of expression of the LDL receptor on mesangial cells has not been extensively evaluated, but inhibitors of intracellular cholesterol synthesis upregulate HMG-CoA reductase. Thus, the LDL receptor likely is also upregulated [58].

Whether mesangial cells possess the so-called "scavenger" receptor is still debated, as binding or internalization of acetylated or oxidized LDL by human mesangial cells was not demonstrated [53]. Binding and uptake of oxidized LDL by rat mesangial cells has been observed, however [53]. Moreover, mRNA for a "scavenger" receptor has been detected in rat mesangial cells [53]. Whether injured mesangial cells increase expression of this receptor is unknown.

Exposure of mesangial cells to LDL appears to evoke a proliferative response (Fig. 2). This proliferation is particularly evident when other growth-promoting factors are present in the tissue-culture medium. An increase in thymidine incorporation accompanied by an increase in mesangial cell number has been consistently observed when mesangial cells are exposed to concentrations of LDL as high as approximately 100–150 μg/ml [55, 58, 59]. In addition, LDL stimulation of the expression of early nuclear response genes *c-fos* and *c-jun* has been described [55]. Increased expression of mRNA for platelet-derived growth factor (PDGF) has been observed in mesangial cells exposed to LDL [55]. Synergistic interactions between LDL and growth-promoting cytokines such as endothelin, PDGF, and IGF-1 (insulin-like growth factor) further support a role of LDL in modulating mesangial cell proliferation [55]. The recent demonstration that PDGF may play a role in mesangial cell proliferation leading to glomerulosclerosis in vivo further underscores the potential importance of these interactions between lipids and growth factors [60, 61].

Influence of lipids on glomerular macrophage recruitment. Previous studies have suggested a relationship between an influx of macrophages and the development of renal disease [62]. We also know that hypercholesterolemia aggravates glomerular macrophage influx in a variety of experimental diseases [63]. Moreover, diet-induced hypercholesterolemia also is associated with a prompt increase in glomerular macrophages [42]. Rovin and Tan recently evaluated the effect of LDL cholesterol on mesangial cell production of a potent monocyte chemotactic factor, monocyte chemoattractant protein (MCP-1) [63]. In these experiments LDL

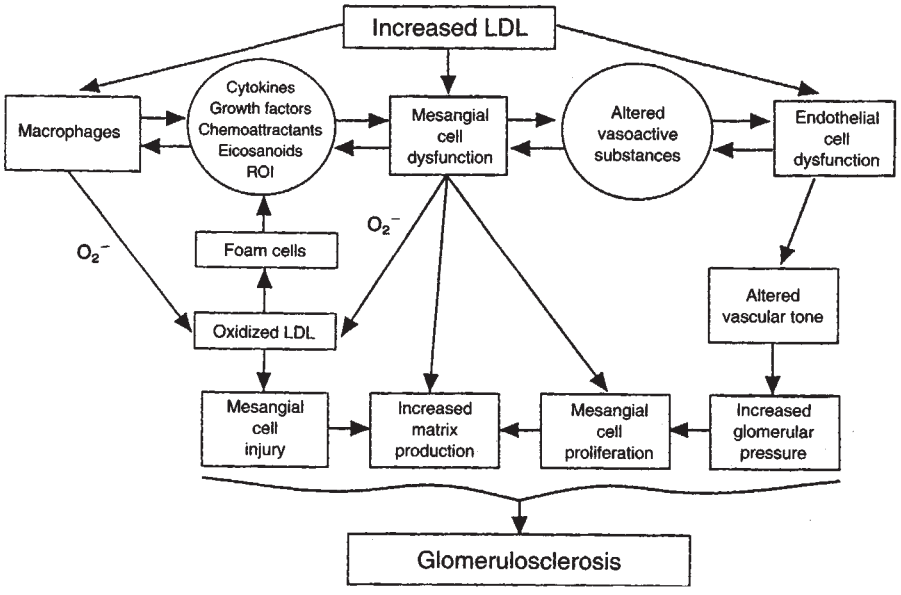

Fig. 2. *The effect of hyperlipidemia on glomerulosclerosis.* Low-density lipoprotein (LDL) can be taken up by mesangial cells and induce mesangial cell proliferation and production of macrophage chemotactic factors. Macrophages as well as mesangial cells can oxidize LDL, thereby leading to the formation of foam cells. Different products released by macrophages and/or foam cells lead to mesangial cell toxicity. Oxidized LDL also has been shown to be injurious to mesangial cells. Conversely, lipid-induced endothelial dysfunction can contribute to altered vascular tone and increased glomerular pressure, which can further modify mesangial cell biology. The increased cellularity and expanded mesangial matrix are the pathologic hallmarks of glomerulosclerosis. (Adapted with permission from *Curr Opin Nephrol Hypertens* 2:372–379, 1993.)

cholesterol increased the expression of MCP-1 mRNA, as well as the secreted protein in a dose-dependent manner [63]. Preliminary studies from our laboratory have suggested that minimally oxidized LDL also stimulates expression of MCP-1 mRNA by human fetal mesangial cells (unpublished observations). These studies suggest that one mechanism whereby hyperlipidemia might influence glomerular injury is through recruitment of macrophages, possibly mediated by increased MCP-1 production (Fig. 2).

Influence of lipids on mesangial matrix. Mesangial matrix expansion occurs in lipid-mediated glomerular injury, and antilipemic therapy reduces the degree of mesangial expansion [1, 42]. These data collectively suggest that lipids might modulate accumulation of matrix proteins. Whether this modulation was a direct effect of lipids on mesangial cell matrix production and/or degradation, or an indirect effect possibly mediated through macrophage recruitment, is unknown. In one recent study, the addition of LDL to mesangial cell cultures increased mRNA for, and synthesis of, fibronectin [63]. We have evaluated the effect of LDL alone and LDL in concert with IGF-1 on mRNA expression of proteins involved in the synthesis and degradation of type-IV collagen and found that each substance alone increased mesangial cell α_1 chain type-IV collagen mRNA, but that the two together did not cause an additive stimulation of its expression (unpublished observations). Moreover, mesangial cells exposed to IGF-1 and LDL alone or in combination displayed an increase in a tissue inhibitor of metalloproteinases (TIMP-2) without producing any effect on the mRNA for the 72 kD collagenase for type-IV collagen. These results suggest that LDL alone or in concert with IGF-1 influences mesangial cell type-IV collagen synthesis as well as its degradation (Fig. 2). The influence of LDL in concert with other cytokines that influence mesangial expansion such as PDGF or TGF-β remains to be established. However, it has been shown in hypercholesterolemic nephrotic rats that increased glomerular fibronectin mRNA expression is associated with increased TGF-β expression by infiltrating macrophages [64].

Oxidative modification of LDL by mesangial cells. Recent studies suggest that modifications (especially by oxidation) in the structure of lipoproteins can affect the potential for vascular injury [65, 66]. Indirect evidence implies that modification of LDL might participate in glomerular injury. These lines of evidence include an increased concentration of cholesterol esters in cortical tissue of hypercholesterolemic rats and guinea pigs; increased glomerular foam cells in proteinuric renal diseases and in cholesterol-fed rats; and increased glomerular deposition of apolipoproteins and oxidized lipoproteins in hypercholesterolemic rats with nephrotic syndrome secondary to the puromycin aminonucleoside [1, 2, 67]. Monocyte/macrophages have been shown to oxidatively modify LDL [68]. Recently, it has been demonstrated that proliferating mesangial cells can oxidatively modify LDL by a mechanism that involves generation of reactive oxygen species [58, 59]. It is interesting that oxidized LDL inhibited mitogen-induced mesangial cell proliferation [58, 59]. In addition, oxidized LDL is a chemoattractant for macrophages and can induce MCP-1 mRNA in a variety of cell types [68]. The precise role that oxidized LDL plays in experimental models of progressive renal disease is unclear but, as I mentioned earlier, the use of antioxidants such as probucol has been associated with amelioration of renal injury [50].

Effects of lipid-lowering agents on mesangial cells. Antilipemic agents, such as HMG-CoA reductase inhibitors, reduce circulating lipids, and this reduction is associated with a proportional amelioration of glomerular injury. Whether this class of agents influences cellular processes associated with injury has only recently begun to be explored. Inhibitors of the enzyme HMG-CoA reductase, such as lovastatin, block the intracellular production of mevalonate and its metabolites (Fig. 3). Products of intracellular mevalonate metabolism are critical for the growth and proliferation of eukaryotic cells [69]. These products include cholesterol and several nonsterol isoprenoids. The isoprenoid farnesyl, a particularly important intermediate in the mevalonate pathway, can be used to synthesize cholesterol and also can bind covalently to several low-molecular-mass GTP-binding proteins such as p21 ras. Farnesylated p21 ras might be critical for

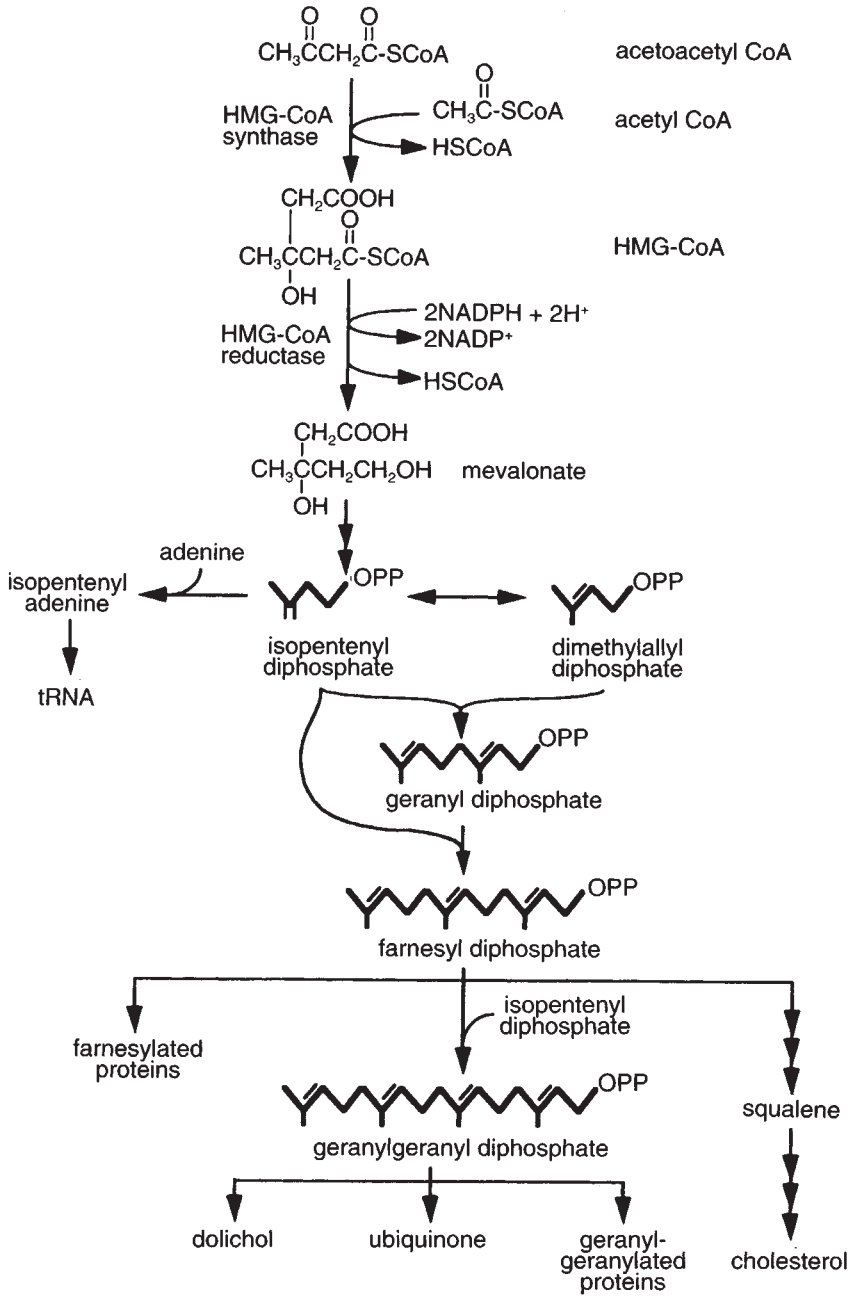

Fig. 3. *The mevalonate pathway.* Mevalonate is synthesized from acetyl coenzyme A, phosphorylated to produce mevalonate diphosphate (not shown), and then metabolized to a series of isoprenoid intermediates. Farnesyl diphosphate occupies an important central location in the pathway, being routed to many end products necessary for cell viability and proliferation. (Reprinted from Ref. 71; © S. Karger AG, Basel.)

mitogenic signaling stimulated by growth factors such as PDGF [70]. In addition, this farnesylated p21 ras-growth factor receptor complex appears to activate nuclear transcription factors such as NF-κB and NF-IL-6 (Fig. 4), which are involved in the regulation of gene expression for MCP-1 and IL-6 [71]. We recently demonstrated that lovastatin inhibited serum-induced proliferation of mesangial cells [72]. Lovastatin inhibition was reversed by the simultaneous addition of either mevalonate or farnesol, but not by exogenous LDL cholesterol. We have also demonstrated that lovastatin inhibits PDGF-induced mesangial cell mitogenesis and that this inhibition could be reversed by either mevalonate or farnesyl pyrophosphate [73]. Additional support for a role of this isoprenoid in modulating the mitogenic effect of PDGF comes from experiments in which mesangial cells were treated with perillic acid, which inhibits farnesylation of intracellular proteins such as p21 ras. In these studies, perillic acid caused a significant dose-dependent inhibition of PDGF-stimulated DNA synthesis.

Because serum-induced mesangial cell mitogenesis also influences nuclear transcription factors involved in cellular expression of MCP-1 and IL-6, we also evaluated the influence of lovastatin on mesangial cell production of MCP-1 and IL-6. Lovastatin significantly inhibited both MCP-1 and IL-6 mRNA expression and secretion of the proteins in a dose-dependent manner [74]. These effects were reversed by exposure of mesangial cells to exogenous mevalonate. By contrast, doses of lovastatin that markedly inhibited MCP-1 and IL-6 production had no effect on

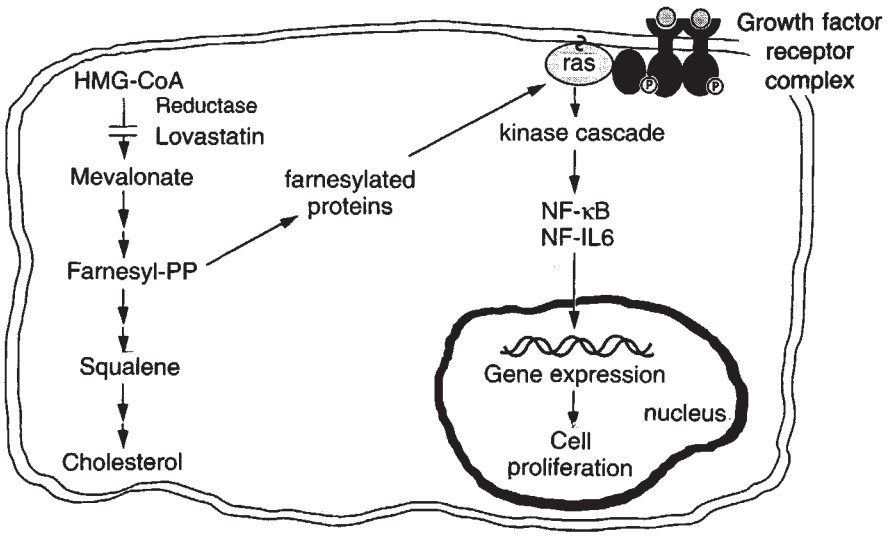

Fig. 4. *Relationship between isoprenoid intermediates and cell signaling by growth factors, that is, PDGF.* Inhibition of HMG-CoA reductase by lovastatin might influence mesangial cell proliferation by reducing such isoprenoid intermediates as farnesyl pyrophosphate (PP), thereby reducing farnesylation of proteins such as p21 ras necessary for the initial signal transduction by certain growth factor receptors.

mesangial cell expression of TGF-β [74]. These data suggest that the in-vivo beneficial effects of lovastatin in models of renal disease might be related, in part, to this agent's ability to ameliorate glomerular macrophage recruitment and to modulate the mesangial cell's proliferative response to mitogenic cytokines.

Summary

In summary, increasing clinical data suggest a relationship between progressive, proteinuric renal disease and abnormal lipid metabolism. These lipid abnormalities might contribute not only to the increased prevalence of cardiovascular disease in these patients, but also to the progressive loss of renal function. Experimental data supporting this concept have rapidly expanded, but studies to test this hypothesis in humans are lacking.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): In view of the similarities between atherosclerosis and glomerulosclerosis, could you summarize for us what's known about the LDL receptor and its regulation in the mesangial cell and the glomerular foam cell?

DR. KEANE: The LDL receptor is present on both rat and human mesangial cells. The regulation of the LDL receptor appears to be similar to the regulation of the LDL receptor that is present in other cell types (for example, hepatocyte, peripheral blood mononuclear cells), and it appears to be tightly linked to HMG-CoA reductase activities. As you might expect, inhibition of HMG-CoA reductase enzymes upregulates the LDL receptor in both glomerular mesangial and epithelial cells.

Foam cells are derived from peripheral blood mononuclear cells and behave in a different fashion than do purified, normal monocytes. Their ability to generate cytokines and various eicosanoid mediators appears to be increased compared to normal monocytes. The foam cell might have some important biologic effects within the glomerulus. Jonathan Diamond recently demonstrated in-vivo function of monocytes (using immunohistochemical stains for a variety of cytokines) in experimental models of proteinuric renal diseases in which lipids appear to play a role [64].

DR. MADIAS: Is the mechanism of oxidation of LDL by the mesangial cell similar to that described in other cells?

DR. KEANE: Proliferating mesangial cells probably can oxidize native LDL. The oxidation of LDL by mesangial cells appears to be related to the generation of free radicals, particularly superoxide and hydroxyl molecules. The mechanism of formation of free radicals by mesangial cells is not completely understood. Both the lipoxygenase pathway and the CP450 oxidative pathway have been proposed as potential mechanisms.

DR. MADIAS: Recognizing that mesangial hypercellularity is not equivalent to mesangial proliferation, could you expand on the nature of the hypercellularity observed in animal studies of diet-induced hypercholesterolemia, namely, on the time course of the appearance of mesangial proliferation and macrophage infiltration?

DR. KEANE: I can only comment on the infiltrating monocytes. This infiltration occurs within 7 days after initiation of a cholesterol-rich diet. Whether mesangial cells are proliferating before the influx of monocytes is unknown.

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): Could you expand on your comments regarding Keilani's study of the effects of fosinopril [16]? I'm not sure I understood the observations. Second, what is your understanding of the mechanisms of those observations?

DR. KEANE: The point of those observations was related to the role of proteinuria in causing lipid abnormalities. Proteinuria induces an abnormality that affects the synthesis and degradation of lipoproteins. Reduction in proteinuria, in this case by an ACE inhibitor, reduced the hyperlipidemia independent of effects on serum albumin.

DR. HARRINGTON: Where precisely does the ACE inhibitor act in this regard?

DR. KEANE: I think the modulation occurs because of its effect on reducing proteinuria. I'm unaware of any other effects of ACE inhibitors directly on lipid metabolism.

DR. HARRINGTON: Ten to 15 years ago, we were first told about the potential beneficial effect of protein restriction in renal disease. Given the relative failure of the recently completed MDRD study, what will it take to prove that lowering serum lipid

levels has a beneficial effect on the progression of renal disease? What study would you envisage?

DR. KEANE: I could envision a study performed in high-risk patients, that is, patients at increased risk for progression such as those with substantial proteinuria and hyperlipidemia. This group might be the ideal subset of patients to study. The MDRD data should provide us with risk factors and, perhaps, let us know which patients are consistently rapid progressors. In this time of health care reform, however, we might not have the money available for large trials. My bias would be to do a limited trial with a well-defined population that has well-defined risk factors.

DR. MADIAS: One would anticipate that experimental impairment of antioxidant defense mechanisms would aggravate the glomerulosclerosis resulting from feeding cholesterol-rich diets. Have such studies been done?

DR. KEANE: Rats fed a vitamin E- and selenium-deficient diet, which depletes antioxidant defenses, are at increased risk for developing lipid-induced vascular injury [75]. Whether this increases renal injury has not been completely evaluated.

DR. ANDREW KING (*Division of Nephrology, New England Medical Center*): One example of a high LDL state in humans is type-1 hypercholesterolemia, in which the LDL cholesterol receptor is absent. Although these patients have accelerated atherosclerosis, they have no major glomerular lesions. Is this because they don't have primary renal disease, glomerular injury, or some other factor? I am also interested in other forms of human hyperlipidemia, some of which are associated with glomerular changes, but most of which are not.

DR. KEANE: Lipids do not appear to be an initiator of clinically overt renal disease. But I'm not convinced that hyperlipidemia in humans does not induce any changes within the glomerulus at all. A number of years ago Bert Kasiske looked at hypercholesterolemia and atherosclerosis and found a significant correlation between hypercholesterolemia and the development of global glomerular sclerosis [76]. Another piece of information, in the diabetic literature, is the relationship between heart disease in the parents and diabetic nephropathy in the children [77]. This gives some credibility to the hypothesis that the abnormal metabolic milieu of hyperlipidemia might facilitate the development of both atherosclerosis and glomerulosclerosis.

DR. HARRINGTON: You reviewed the studies investigating the effects of LDL on mesangial cell proliferation. Do you have comparable studies on macrophages?

DR. KEANE: We have not studied the macrophage from glomeruli. Macrophages have LDL receptors and behave similarly to other cells. I am unaware of data that have evaluated the effects of HMG-CoA reductase inhibitors on glomerular macrophage function.

DR. HARRINGTON: Do you have a direct way of reducing Lp(a) without affecting other cholesterol abnormalities?

DR. KEANE: I wish I did. Nicotinic acid has been used. A number of ongoing studies are looking at the newer fibrate derivatives to see how they might influence Lp(a). Most of the antilipemic agents do not have a significant effect on Lp(a). Reduction of proteinuria has been associated with a reduction in Lp(a), together with other lipids.

DR. BRIAN PEREIRA (*Division of Nephrology, New England Medical Center*): In some of the studies that you discussed, high lipid levels were associated with progression of renal disease. Is proteinuria, which also was associated with progressive renal disease, an independent risk factor?

DR. KEANE: In the studies reported to date, hypertension and hyperlipidemia were identified as independent risk factors by multivariate analysis. The dyslipidemia also was independent of proteinuria. The MDRD study will provide additional insights in this regard.

DR. PEREIRA: Is it possible that the elevated lipid levels are immunostimulatory as far as peripheral blood mononuclear cells are concerned? In that case, anti-lipid strategies would exacerbate the immunodeficiency of uremia.

DR. KEANE: I don't know. I'm unaware of any studies of the immune response in patients who have hyperlipidemia.

DR. AJAY SINGH (*Division of Nephrology, New England Medical Center*): You postulated that lipids modulate mesangial cell proliferation through the secretion of a variety of cytokines, including IL-6. Could you review the mechanisms by which lipids might modulate the regulation and secretion of inflammatory cytokines? Are other cells, such as macrophages, involved in this response? Is activation by IgG immune complexes binding to Fc receptors on mesangial cells a prerequisite for lipid-induced mesangial cell cytokine release?

DR. KEANE: Lipids appear to function as a competence factor for a variety of cytokines that induce proliferation of mesangial cells. As such, many of these cytokines can induce, in an autocrine manner, mesangial cell production of these cytokines. It is also clear that macrophages are involved in the initial production of these inflammatory mediators. What is unknown is how these mediators are chronically produced and by what cell type. I suspect that an initial toxic or immunologic insult in the glomerulus is the first step, which is followed by an influx of inflammatory cells. The stimulus for this influx might be mesangial cell release of certain inflammatory cytokines, for example, MCP-1 or CSF. These macrophages possibly amplify any inflammatory response and ultimately lead to resolution of the disease. In some settings, however, resolution does not occur and chronicity leads to nephron loss. It is unclear at present what leads to this chronic progressive phase. As I suggested, modified lipids could be one such factor; it would appear that they can stimulate production of key cytokines such as TGF-β.

DR. SINGH: Does regulation of TGF-β involve the HMG-CoA reductase pathway?

DR. KEANE: No. There is no evidence that inhibition of HMG-CoA reductase modifies expression of TGF-β by mesangial cells.

DR. SINGH: How, then, does lovastatin, an HMG-CoA reductase inhibitor, modulate TGF-β gene regulation? Is there another pathway?

DR. KEANE: It is possible that lovastatin influences macrophage recruitment by its ability to decrease MCP-1 production. This, in turn, could influence macrophage production of TGF-β in the glomerulus indirectly.

DR. RICHARD LAFAYETTE (*Division of Nephrology, New England Medical Center*): The ability of anti-lipemic therapy to be antiproliferative might allow it to protect against renal injury by reducing glomerular hypertrophy. Has a reduction in glomerular hypertrophy been found in studies of progressive renal disease when anti-lipemic therapy is used?

DR. KEANE: We have looked at glomerular hypertrophy. Our results are not impressive in terms of reducing compensatory

hypertrophy. Reduction of hypertrophy doesn't seem to be a major component of the mechanism of action of these antilipemic agents.

DR. MADIAS: Are there comparative studies on the salutary effects on the kidney of a nonabsorbable hypolipemic agent, such as cholestyramine versus HMG-CoA reductase inhibitors, that weigh the relative importance of the nonhypocholesterolemic effects of the latter class of agents?

DR. KEANE: Cholestyramine has been used, and this agent has reduced glomerular injury. I'm not sure whether solid comparative studies are available.

DR. JULIA NEURINGER (*Division of Nephrology, New England Medical Center*): You showed that lovastatin reduces intimal proliferation in the aorta in a model of chronic vascular rejection. Are you aware of any data showing a correlation between cholesterol levels and progression in renal transplant patients? Have you tried giving lovastatin to any of your patients?

DR. KEANE: Kasiske's study looked at risk factors for chronic renal rejection and found an association with cholesterol levels and evidence for chronic rejection one year post transplantation [78]. He currently has a prospective trial of an HMG-CoA reductase inhibitor in transplant patients, but I have no results to date.

DR. MADIAS: Can you give us your recommendations about treating the dyslipidemia of the nephrotic syndrome and that of chronic renal failure?

DR. KEANE: I've given my bias with transplant patients because cardiovascular disease and chronic vascular rejection are the most important complications in the transplant patient, and hypercholesterolemia is common in these patients. I believe it is appropriate to treat these patients with an HMG-CoA reductase inhibitor. In patients with chronic, persistent proteinuria and hypercholesterolemia, my own prejudice is that we should treat unless there is a contraindication. While others have successfully reduced cholesterol levels by dietary modification in patients with the nephrotic syndrome, we have been relatively unsuccessful in changing hypercholesterolemia with our dietary approaches. We do use dietary modification, but we usually add low doses of an HMG-CoA reductase inhibitor after attempting to reduce proteinuria.

DR. SVETLOZAR N. NATOV (*Clinical Research Fellow, Division of Nephrology, New England Medical Center*): Cyclosporine is known to disturb the balance between vasodilatory and vasoconstrictive eicosanoids [79] and to cause hypertriglyceridemia [80]. At the same time, omega-3 polyunsaturated fatty acids (fish oil) have been found of therapeutic benefit in CsA-treated renal transplant recipients and in patients with chronic glomerular disease, probably because these compounds have favorable effects on prostaglandin synthesis and lipid metabolism [81, 82]. Would you give us your experience with fish oil in renal diseases and, more particularly, in cyclosporine-treated transplant recipients?

DR. KEANE: I don't have any personal experience using fish oils in patients with renal disease. A number of reports show that fish oils have benefit in a variety of different diseases, one of which is cyclosporine-induced injury. How the fish oils work is unclear. There is no question that in animals and humans the oils affect circulating lipids, particularly circulating triglyceride levels. Fish oils also have a host of effects on eicosanoid production and cytokine production, which, in turn, may influence and modulate renal injury.

Reprint requests to Dr. W. Keane, Department of Medicine, Division of Nephrology, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, Minnesota 55415, USA

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